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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/832,069	04/10/2001	Marschall S. Runge	CLFR:183US	8710

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EXAMINER	
GOLDBERG, JEANINE ANNE	

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 04/05/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/832,069	RUNGE ET AL.	
	Examiner	Art Unit	
	Jeanine A. Goldberg	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 January 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *6,8,9 and 14-23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *6,8,9 and 14-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to the papers filed July 5, 2005. Currently, claims 6, 8-9, 14-23 are pending.

2. All arguments have been thoroughly reviewed but are deemed non-persuasive for the reasons which follow. This action is made FINAL.

3. Any objections and rejections not reiterated below are hereby withdrawn.

Maintained Rejections

Claim Rejections - 35 USC § 112-Scope of Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

1. Claims 6, 16-20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for measuring the amount of oxidative stress in an individual by detecting the amount of DNA damage per length of DNA using QPCR, does not reasonably provide enablement for detecting mtDNA damage by measuring mitochondrial mRNA production, mitochondrial protein production, mitochondrial oxidative phosphorylation, mitochondrial ATP production or mitochondrial redox state. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and breadth of claims

The claims are drawn to a method for measuring the amount of oxidative stress in an individual by detecting the amount of DNA damage per length of DNA using QPCR, detecting mtDNA damage by measuring mitochondrial mRNA production, mitochondrial protein production, mitochondrial oxidative phosphorylation, mitochondrial ATP production or mitochondrial redox state.

The invention is a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The unpredictability of the art and the state of the prior art

The art teaches that tissue ischemia, OXPHOS gene defects, environmental toxins, mtDNA mutations, decreased cellular ATP and oxygen radical formation all affect oxidative phosphorylation dysfunction which leads to tissue degeneration and cell

death (Corral-Debrinski et al. 1992). The art does not teach how the amount of mtDNA damage is affected or associated by each of these factors.

Guidance in the Specification.

The specification states "a person having ordinary skill in this art would recognize that measurement of mitochondrial DNA damage is only one potential method to determine oxidative stress. Any downstream or resultant effect of mitochondrial DNA damage will reflect the same disease process. For example, measurement of mitochondrial protein production, changes in mitochondrial ATP production would accomplish the same goal. The specification provides no evidence teachings regarding the relationship between mtDNA damage and mitochondrial mRNA production, mitochondrial protein production, mitochondrial oxidative phosphorylation, mitochondrial ATP production or mitochondrial redox state. The specification does not teach how these measurements are associated. A mutation in mtDNA may cause such problems with the mtDNA damage that there is no protein production, for example. Thus, measuring protein production of zero due to a truncation mutation would not provide any guidance of the quantity of DNA damage. Since only one mutation may completely negate the protein production, it is unpredictable that this would provide the skilled artisan with the amount of mtDNA damage present. Alternatively, the lesions or mutations/damage may occur in non-coding regions which do not affect protein. The specification has not taught that there is any direct tie. Similarly, the specification does not provide any links between mitochondrial mRNA production, mitochondrial oxidative phosphorylation, mitochondrial ATP production or mitochondrial redox state. Reduced ATP could be a single lesion and not due to a larger number of quantitative lesions in

the genome. The knockout of mitochondrial enzyme with a single mutation could cause dysfunction.

The guidance provided by the specification amounts to an invitation for the skilled artisan to try.

Working Examples

The specification has no working examples of measuring the *amount* of mtDNA damage in tissue using mitochondrial mRNA production, mitochondrial protein production, mitochondrial oxidative phosphorylation, mitochondrial ATP production or mitochondrial redox state.

Quantity of Experimentation

The quantity of experimentation in this area is extremely large since there is significant number of parameters which would have to be studied. As discussed above, there is no guidance or teachings in the specification how measurements of the amount of mtDNA damage in a tissue is associated with mitochondrial mRNA production, mitochondrial protein production, mitochondrial oxidative phosphorylation, mitochondrial ATP production or mitochondrial redox state. There are many other factors which would affect each of theses quantities which may not be related to amount of mtDNA damage. This would require years of inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

In the instant case, as discussed above, in a highly unpredictable art where the specification and the art does not teach how the amount of mtDNA in a tissue may be associated with mitochondrial mRNA production, mitochondrial protein production, mitochondrial oxidative phosphorylation, mitochondrial ATP production or mitochondrial redox state. Further, the prior art and the specification provides insufficient guidance to overcome the art recognized. Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the absence of a working example and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Response to Arguments

The response traverses the rejection. The response asserts that the art does teach how the amount of mtDNA damage is affected or associated with each of the factors in question. The response cites articles including Lenaz, Hudson and Williams. The response asserts that the Lenaz article teaches a vicious cycle however, the "vicious cycle" in Lenaz does not provide any guidance into how the mtDNA encoded protein is indicative of oxidative stress in an individual, as required by the instant claims. Moreover, the "vicious cycle does not appear to contain information regarding detecting mtDNA damage by measuring mitochondrial mRNA production,

mitochondrial oxidative phosphorylation, mitochondrial ATP production or mitochondrial redox state. Furthermore, Hudson does not provide any guidance into how mtDNA damage may contribute to a decline in the rate of mitochondrial protein synthesis. Hudson teaches "a decrease in mitochondrial cytochrome c oxidase (COX) activity associated with a reduction in COX gene and protein expression and a similar decrease in the rate of mitochondrial protein synthesis. Damage to mitochondrial DNA *may* contribute to this decline. However, Hudson does not appear to contain information regarding detecting mtDNA damage by measuring mitochondrial mRNA production, mitochondrial oxidative phosphorylation, mitochondrial ATP production or mitochondrial redox state. Hudson acknowledges the relatively few reports regarding occurrence of mtDNA damage and suggests a comprehensive and long-ranged study to determine the true impact. Thus, the teachings of Hudson does not appear to fill the gap in information regarding how the different measurements are associated and/or indicative of oxidative stress. The last article cited is Williams which is directed to "altered mitochondrial function". Upon review of Williams, the article similarly does not contain information regarding detecting mtDNA damage by measuring mitochondrial mRNA production, mitochondrial oxidative phosphorylation, mitochondrial ATP production or mitochondrial redox state.

The response asserts that the action fails to set forth evidence of unpredictability. Based upon both lack of teachings in the specification, the lack of teachings in the art prior to the filing date, the examiner has based the determination of unpredictability. The lack of art that provides a correlation is evidence of the lack of guidance provided in

the art. The examiner and the applicant appear both to have searched the art for the correlation, but do not appear to have any evidence to indicate an association regarding detecting mtDNA damage by measuring mitochondrial mRNA production, mitochondrial protein production, mitochondrial oxidative phosphorylation, mitochondrial ATP production or mitochondrial redox state.

In view of the amendments to the claims to require a blood sample, the rejection as it is drawn to particular mitochondria has been withdrawn. However, it remains unclear how the ordinary artisan would assess ATP production, for example and provide an indication of oxidative stress in an individual to obtain a measure of the amount of oxidative stress in a human individual, as required by the instant claims.

Thus for the reasons above and those already of record, the rejection is maintained.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 6, 8-9, 14-23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 6, 8-9, 14-23 are indefinite because it is unclear whether the final clause of the method is directed to detecting amount of damage or mere presence of damage. The claim states, "wherein such damage is indicative of oxidative stress in

said individual." Thus, the claim does not particularly appear to require establishing a correlation based upon any amount or ration or other measurement of quantity of damage.

Response to Arguments

The response traverses the rejection. The response asserts the claim has been amended to require assessing the amount. This argument has been considered but is not convincing because the claim remains drawn to a method where once the artisan has "assessed" or measured the amount of mtDNA damage the information is indicative of oxidative stress. However, the claim lacks any guidance or process step which provides the artisan how the amount or assessment is indicative of oxidative stress. Thus for the reasons above and those already of record, the rejection is maintained.

New Grounds of Rejection

B) Claim 23 is indefinite over the recitation "the hematopoietic cell" because Claim 6 has been amended to no longer require a hematopoietic cell. Therefore, the hematopoietic cell lacks proper antecedent basis. Appropriate correction is required.

Conclusion

2. **Claims 6, 8-9, 14-23 are rejected.**

3. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP

§ 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

4. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (571) 272-0743. The examiner can normally be reached Monday-Friday from 7:00 a.m. to 4:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on (571) 272-0735.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

The Central Fax Number for official correspondence is (571) 273-8300.

J. Goldberg

Jeanine Goldberg
Primary Examiner
April 3, 2006